Remarks

Claims 27-38, 45-50, 57-62 and 81-86 are pending in the application, with claims 27, 33, 45, 57 and 81 being the independent claims.

The present application is a divisional of U.S. Application No. 08/741,095, filed October 30, 1996, and claims the benefit of the filing dates of International Application No. PCT/US95/05058 (the '058 application), filed April 27, 1995, and U.S. Application Nos. 08/464,595 (the '595 application), 08/462,962 (the '962 application), and 08/462,315 (the '315 application), each of which was filed June 5, 1995. In addition, all of the above noted applications are incorporated by reference into the present application.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Status of Application, Amendments and/or Claims

The Examiner indicated that the amendment filed on March 31, 2001 (Paper No. 11) was entered in full and that claims 27-38, 45-50, 57-62 and 81-86 were pending and under examination. (*See* Paper No. 14, page 2.)

Withdrawn Objections and/or Rejections

Applicants thank the Examiner for withdrawing all previously made objections and/or rejections. (*See* Paper No. 14, page 2.)

New Matter

The Examiner objected to the amendment filed on June 29, 1999 (Paper No. 3) under 35 U.S.C. § 132 for allegedly introducing new matter into the disclosure. Particularly, it is the Examiner's position that the addition of Example 7 is not supported by the original disclosure and that Applicants are required to cancel the new matter in reply to the Office Action. (*See* Paper No. 14, page 2.)

In support of the above objection, the Examiner asserts that

> Applicant indicates in the amendment cited above that the information is "essentially the same" as specific portions of parent application PCT/US95/05058, which has been properly incorporated by reference. However, this parent PCT application is in a foreign language, and no certified translation of the document could be found in the instant U.S. Application. Therefore, the official record does not show clear support for the added material, and a new matter objection is proper. Applicant is encouraged to provide a certified translation of PCT/US95/05058 so that the new matter issues can be resolved.

(Paper No. 14, pages 2-3.) Contrary to the Examiner's assertions, the '058 application is not in a foreign language (copy of the published application, *i.e.* Int'l Pub. No. WO 96/34095, is attached as Exhibit A). Rather, the application was filed in English.

The specification of the captioned application was amended to introduce subject matter from the '058 priority application which, as noted by the Examiner, has been properly incorporated by reference into the captioned application. In particular, Example 7, which is essentially the same as Example 4 of the '058 application, has been added to the specification.

Applicants note that "an applicant may incorporate by reference the prior application by including, in the continuing application-as-filed, a statement that such specifically enumerated prior application or applications are 'hereby incorporated herein by reference.' The inclusion of this incorporation by reference of the prior application(s) will permit an applicant to amend the continuing application to include any subject matter in such prior application(s), without the need for a petition." Changes to Patent Practice and Procedure, 62 Fed. Reg. 53132, 53146 (October 10, 1997). As previously asserted, the Examiner has acknowledged that the '058 application was properly incorporated by reference. As such, "[t]he information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter." M.P.E.P. § 2163.07(b) at 2100-128 (Seventh edition, Revision 1, February 2000).

Since the official record does show clear support for the added material, a new matter rejection is improper. Accordingly, Applicants respectfully request that the objection to the amendments under 35 U.S.C. § 132 be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph - New Matter

The Examiner rejected claims 27-32 and 81-86 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the

inventors had possession of the claimed invention at the time the application was filed. (*See* Paper No. 14, page 3.) Specifically, the Examiner asserts that

> [t]he record indicates that SEQ ID NO: 25 and 26 are originally disclosed in PCT/US95/05058, which is a parent of the instant application, the disclosure of which has been properly incorporated by reference. The subsequent sequence listings submitted in the instant applications [sic] which list SEQ ID NOS: 25 and 26 were not objected to as containing new matter, since the foreign language PCT application clearly had support for the sequences *per se*. However, the instant U.S. Application never discusses the molecules represented by SEQ ID NO: 25 or 26 and contains no written description of the inventions represented by the instant claims. . . . Although the parent PCT application PCT/US95/05058 my [sic] be relied upon to provide written description support for the invention claimed in the instant application . . . the PCT application is in a foreign language, and no certified English translation can be found in the instant file. Therefore, it is not clear from the official record where the instantly claimed invention finds it [sic] written description.

(Paper No. 14, pages 3-4.) Applicants respectfully traverse this rejection.

Similar to the objection under 35 U.S.C. § 132, the Examiner bases the rejection of claims 27-32 and 81-86 under 35 U.S.C. § 112, first paragraph, on the assumption that the '058 application is in a foreign language. However, as shown in Exhibit A, the '058 application was filed in English. One skilled in the art reviewing, for example, SEQ ID NOs:1 and 2 and page 37, lines 1-25, of the '058 application would clearly recognize that Applicants were in possession of nucleic acid molecules encoding amino acid -38 to 162 of SEQ ID NO:26 in the captioned application, as well as nucleic acid molecules encoding amino acids 1 to 162 of SEQ ID NO:26.

Consequently, one skilled in the art after reviewing the official record would clearly recognize that Applicants were in possession of the claimed invention. As such, Applicants

respectfully request that the rejection of claims 27-32 and 81-86 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. §§ 101 and 112, First Paragraph - Utility

The Examiner rejected claims 27-38, 45-50, 57-62 and 81-86 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility. (*See* Paper No. 14, page 4.) Specifically, the Examiner asserts that

> [t]he claims are directed to isolated TNF receptor-like 2 (TR2) polypeptides corresponding to SEQ ID NO: 26, or encoded by cDNA clones deposited as ATCC Nos. 97059, 97058, or 97057. The specification never clearly asserts that the TR2 of SEQ ID NO: 26 or encoded by the deposited clones binds a TNF, or mediates any particular effect. The art acknowledges that the TNF receptors mediate diverse and even opposite effects (see specification's review of art at pp. 73-74). Therefore, no specific biological activity has been established for the TR2 of SEQ ID NO: 26 or the deposited clones.

(Paper No. 14, pages 4-5.) Applicants respectfully traverse this rejection.

To satisfy the requirements of 35 U.S.C. § 101, an Applicant "must show that the claimed invention is 'useful' for some purpose either explicitly or implicitly." M.P.E.P. § 2107 at 2100-24 (Seventh edition, Revision 1, February 2000). Furthermore, Applicants respectfully submit that definitive proof of an invention's utility is not required under 35 U.S.C. § 101. "In most cases, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101." M.P.E.P. § 2107.01(III.)(A.) at 2100-30 (Seventh edition, Revision 1, February 2000). An assertion

of utility will satisfy the requirement of 35 U.S.C. § 101 unless "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion." M.P.E.P. § 2107.01(III.)(B.) at 2100-31 (Seventh edition, Revision 1, February 2000).

In addition, Applicants "need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement." Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098 (January 5, 2001). Additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility. *See, e.g., Raytheon v. Roper*, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown."). Accordingly, if Applicants make one credible, specific and substantial assertion of utility, utility for the claimed invention as a whole is established.

Applicants further note that "[c]redibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098 (January 5, 2001). In addition, "a *prima facie* showing of no specific and substantial credible utility must establish that it is *more likely than not* that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention." *Id.* (emphasis added). Applicants respectfully submit that the disclosure and evidence of record would be sufficient to lead one skilled in the art to conclude that the asserted utilities are more likely than not true and that the Examiner has not met the burden necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101.

The Examiner is requiring an explanation of the logic underlying the asserted utility. However, "'[i]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works.' *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir.1989); *see also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983) ('[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.')." *In re Cortright*, 49 U.S.P.Q.2d 1464, 1469 (Fed. Cir. 1999). Nevertheless, Applicants submit that not only is the logic underlying these assertions scientifically sound, but that the facts upon which the assertions are based are consistent with the logic underlying the assertions.

There are several statements in the '058 application that fully and clearly set forth Applicants' assertions of the TR2 receptor's biological role and explain why the Applicants believe the invention is useful. In general, the "invention relates to TNF receptor, the amino acid sequence of which is set forth in SEQ ID NO:2." (The '058 application, page 6, lines 24-25.) In addition, "[t]he TNF receptor and the two splice variants belong to a family of receptors and antigens known as the Nerve Growth Factor/Tumor Necrosis Factor Family." (The '058 application, page 4, lines 1-3.) As disclosed in the '058 specification at page 7, lines 16-17, the TR2 receptor "is structurally related to the human NGF/TNF receptor family." (The '058 application, page 7, lines 12-17.) In particular, "[t]he receptor polypeptides of the present invention show significant amino acid sequence homology to the type 2 human tumor necrosis factor receptor." (The '058 application, page 4, lines 13-16; *see also* Figure 2.) In fact, "[t]he protein exhibits the highest degree of homology to a human type 2 TNF receptor with 32% identity and 44% similarity over a 117 amino acid stretch." (The '058 application, page 7, lines 21-23.) Moreover, the type 2 TNF receptor is

known "to exclusively mediate human T cell proliferation by TNF as shown in PCT Publication No. WO 94/09137." (The '058 application, page 3, lines 24-26.)

Based in part on this homology, it is asserted that the TR2 polypeptide of the present invention has biological effects and activities similar to type 2 TNF receptor. For example, it is asserted that within the scope of the invention there are provided processes of using "agonists for treating conditions related to insufficient activity of the polypeptide of the present invention, for example, . . . to stimulate human cellular proliferation, e.g., T-cell proliferation." (The '058 application, page 5, lines 13-16; *see also* the '058 application at page 20, line 25, to page 21, line 6, page 26, lines19-21, and page 27, lines 1-5.) It appears, however, that the Examiner is of the opinion that the TR2 receptor of the present invention and the type 2 TNF receptor do not possess this same functional property. (Paper No. 14, pages 4-5.)

Although homology-based methods for assigning function to proteins are not perfect, perfection or "statistical certainty" of the evidence presented in an application is not required for an assertion of utility to be valid. *See* M.P.E.P. § 2107.01 (VII.) at 2100-33 (Seventh edition, Revision 1, February 2000); *see also Nelson v. Bowler*, 626 F.2d 853, 856-57 (C.C.P.A. 1980). Nor is a "rigorous correlation" required between the evidence provided and the asserted utility. Rather, all that is required under 35 U.S.C. § 101 is that the assertion be "reasonably predictive" of the utility. *See, e.g., Rey-Bellet v. Englehardt*, 493 F.2d 1380 (C.C.P.A. 1974). Evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is *more likely than not* true. *See* M.P.E.P. § 2107.01 (VII.) at 2100-33 (Seventh edition, Revision 1, February 2000).

Contrary to the Examiner's contention, the state of the art shows that credible assertions of utility and function of a protein can be made based on homology studies. For example, Wilson *et al., J. Mol. Biol. 297*:233-249 (2000) (Exhibit B) indicate that "functional class is conserved for sequence identities as low as 20-25%." Figure 7A of Wilson *et al.* demonstrates that two proteins sharing as low as 20% sequence identity have a *greater than 70% chance* of being a member of the same functional class. Other publications further confirm the value of homology studies in predicting protein function. *See, e.g.*, des Jardins *et al.*, *ISMB 5*:92-99 (1997) ("The most successful technique for identifying possible function of anonymous gene products . . . is performing similarity searches against sequence databases."); Holm, L., *Curr. Opin. Struct. Biol. 8*:372-79 (1998) ("By inferring homology between two proteins on the basis of sequence similarity, biologists can confidently predict that protein structure and function have remained similar during evolution.")

Consistent with the teachings in the art, a *per se* rule rejecting homology based assertions of utility (which the Examiner seems to be employing in the instant case) has been explicitly rejected by the USPTO. *See* 66 Fed. Reg. 1092, 1096 (January 5, 2001). Specifically, it is the USPTO's position that

> when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, *and bases the assertion upon homology to other proteins having an accepted utility*, the asserted utility *must* be accepted by the examiner unless the Office has sufficient or sound scientific reasoning to rebut such an assertion. "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient."

Id. (citations omitted) (emphasis added). Thus, "when a class of proteins is defined such that members share a specific, substantial and credible utility, the reasonable assignment of a

new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein." *Id.* In view of the above, Applicants assert that an attack on the asserted utilities of human TR2 receptor based upon its homology to another protein of known function and utility is improper and that it is *more likely than not* that a person skilled in the art would consider credible the specific and substantial utility asserted by the Applicants for the claimed invention.

In fact, the data presented in the instant application confirm that the TR2 receptor is involved in T cell proliferation. As asserted in the specification at page 46, line 28, to page 47, line 2, "[t]he experiments set forth in Example 6 demonstrate that the TR2 receptors of the present invention are capable of inducing the proliferation of lymphocytes. Further, such proliferation can be inhibited by a TR2 protein fragment fused to an Fc antibody fragment." *See also* Kwon *et al.*, *J. Biol. Chem. 272*:14272-14276 (1997) (Exhibit C). This asserted utility has further been confirmed by Harrop *et al.* who showed that monoclonal antibodies raised to TR2 are capable of inhibiting $CD4^+$ T cell proliferation, IL-2, IFN-γ, IL-4 and TNF-α secretion and cell surface receptor expression, indicating that TR2 is involved in the control of optimal T lymphocyte activation. *See* Harrop *et al.*, *J. Immunol. 161*:1786-1794 (1998) (Exhibit D).

Courts have repeatedly found that "mere identification" of the biological or pharmaceutical activity of a compound is beneficial to the public and "adequate proof of any such activity constitutes a showing of practical utility." M.P.E.P. § 2107 (III.) at 2100-26 (Seventh edition, Revision 1, February 2000); *see also Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980). Applicants have identified a biological role for the TR2 receptor of the present invention, *i.e.* mediating human T cell proliferation, which was originally based in part on homology to the TNF-R2 and which has been confirmed in subsequent experiments

not only by Applicants but by third parties. Applicants submit that such evidence constitutes adequate proof of such activity.

In view of the above, Applicants assert that the utilities assigned to TR2 are specific, substantial and credible. Even assuming, *arguendo*, the Examiner has established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that the evidence submitted herewith would be sufficient to lead one skilled in the art to conclude that the asserted utility is more likely than not true, and therefore sufficient to rebut the Examiner's showing. As such, Applicants respectfully submit that the presently claimed invention possesses a specific, substantial and credible utility that constitutes a patentable utility under 35 U.S.C. § 101. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-38, 45-50, 57-62 and 81-86 under 35 U.S.C. § 101.

The Examiner also enumerated and addressed seven assertions of credible, specific and substantial utilities for the claimed polynucleotides disclosed in the specification. (*See* Paper No. 14, pages 5-7.) According to the Examiner, each of the asserted utilities was either not specific and/or substantial. Each of these rejections, however, is based, at least in part, on the Examiner's incorrect assumption that no specific biological activity had been established for TR2. In view of the above, it is clear that the presently claimed invention possesses at least one specific, substantial and credible utility. Accordingly, Applicants submit that the seven asserted utilities enumerated by the Examiner are likewise patentable utilities.

The Examiner further rejected claims 27-38, 45-50, 57-62 and 81-86 under 35 U.S.C. § 112, first paragraph. (*See* Paper No. 14, page 7.) Specifically, it is the Examiner's contention that "since the claimed invention is not supported by either a credible, specific

and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (*Id.*)

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by at least one specific, substantial and credible utility. The Examiner "should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. 101 rejection is proper." M.P.E.P. § 2107 (IV) at 2100-28 (Seventh edition, Revision 1, February 2000). Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be not be maintained.

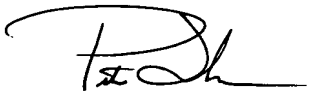
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Peter A. Jackman
Attorney for Applicants
Registration No. 45,986

Date: August 30, 2001

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Attachments: Exhibits A-D